UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,022	05/04/2001	Joseph D. Gold	091/005P	7806

22869 7590 08/27/2003

GERON CORPORATION
230 CONSTITUTION DRIVE
MENLO PARK, CA 94025

EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n N .	Applicant(s)	
	09/849,022	GOLD ET AL.	
	Examiner	Art Unit	
	Thai-An N. Ton	1632	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-12 are pending and under current examination.

Information Disclosure Statement

Applicants' Information Disclosure Statement, filed 12/6/01, Paper No. 7, has been considered.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-22 of copending Application No. 10/039,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods for producing genetically altered primate pluripotent

stem cells and to populations of pPS cells which have been genetically altered. The instant claims are directed to methods for obtaining genetically altered primate pluripotent stem cells by providing a composition of pPS cells essentially free of feeder cells, transferring a polynucleotide into pPS cells in the composition. The '956 claims are directed to methods of producing genetically altered primate pluripotent stem cells comprising providing a composition of pPS cells on a layer of feeder cells that are drug-resistant, transferring a polynucleotide into the pPS cells in the composition and preferentially selecting cells that have been genetically altered with the polynucleotide. Certain of the instant claims differ from the '956 Application in that they are broader. However, all of the instant claims are made obvious by the '956 Application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of obtaining or producing genetically altered primate pluripotent stem [pPS] cells comprising culturing the

pPS cells in a culture environment comprising an extracellular matrix component and a suitable nutrient medium and transfecting the pPS cells with a transgene of interest, does not reasonably provide enablement for methods for obtaining or producing genetically altered pPS cells comprising providing a composition of pPS cells essentially free of feeder cells, and transferring a polynucleotide into pPS cells into the composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to methods of obtaining genetically altered primate pluripotent stem [pPS] cells, or progeny thereof, comprising providing a composition of pPS cells essentially free of feeder cells, and transferring a polynucleotide into pPS cells in the composition. In further embodiments, the claimed invention is direted to methods of producing genetically altered pPS cells or progeny thereof comprising providing a composition of pPS cells on a layer of feeder cells that are drug-resistant, transferring a polynucleotide into pPS cells in the composition and selecting genetically altered cells in the composition using the drug to which the feeder cells are resistant.

The specification teaches methods for culturing primate pluripotent stem [pPS] cells in the absence of feeder cells, and methods of obtaining genetically altered pPS cells by culturing pPS cells on a layer of feeder cells that are drug-resistant, transferring a polynucleotide into pPS cells in the composition, and

selecting genetically altered cells in the composition using the drug to which the feeder cells are resistant. See p. 2, lines 27-41. Particularly, the specification teaches the feeder-free passage of human pluripotent embryonic stem cells. Undifferentiated human embryonic stem cells were cultured in culture wells coated with Matrigel® with conditioned nutrient medium, which was prepared from irradiated mouse embryonic fibroblasts. See Example 1. The specification teaches the *in vitro* and *in vivo* differentiation of the human ES cells. See Example 2. The specification teaches that hES cells that were grown on primary mouse embryonic fibroblasts were transfected with a transgene encoding GFP, and then the cells were analyzed for GFP expression. See Example 3. The specification further teaches that human ES cells were grown on the permanent mouse feeder cell line NHG190, which is a cell line that is immortalized with telomerase, is triple drug resistant and expresses green fluorescent protein [GFP]. The hES cells were transfected by replating the cells in plates precoated with Matrigel® and NHG190 feeder cells and transfecting using the retroviral vector, GRN354, which contains a eGFP encoding region and the neo^r gene driven by the murine PGK promoter. The transfected cells were selected using geneticin selection and the undifferentiated cells that survived selection were maintained for 3 months and express GFP at low levels. See Example 5. The specification further teaches that hES cells, maintained in feeder-free culture on laminin were transfected with a plasmid carrying GFP driven by the CMV promoter. See Example 6.

The state of the art of culturing of primate embryonic stem cells is such that culturing typically requires the presence of feeder cells. Thomson *et al.* discuss the difficulties in culturing pPS in feeder free conditions. Thomson *et al.* (PNAS, 92:7844-7848, 1995) teach the derivation of a cloned cell line from a rhesus monkey that remains undifferentiated when grown on mouse embryonic fibroblast feeder layers, but differentiate or die in the absence of the fibroblasts (see p. 7844, *Abstract*). Particularly, Thomson *et al.* state that in the absence of the feeder layers, soluble human leukemia inhibitory factor (LIF) fails to prevent the differentiation of the cells, and that the factors that fibroblasts produce to prevent the differentiation of the cells is yet unknown (see p. 7847, 1st column, 2nd paragraph). Thomson *et al.* further state that human inner cell mass-derived cells were cultured in the absence of feeder layers failed to survive beyond 2 passages (see p. 7848, 1st paragraph). The instant specification supports Thomson's finding, stating that, "[T]he role of the feeder cells is replaced by supporting the culture (of pPS cells) on an extracellular matrix and culturing the cells in a conditioned medium." See p. 2, lines 6-12. The specification fails to provide or teach any other conditions in which pPS cells could be grown in feeder-free conditions in the absence of an extracellular matrix, as such, the claimed invention is enabling only for culturing the described pPS cells in the presence of an extracellular matrix.

As such, in view of the unpredictable nature of culturing undifferentiated pPS cells in any particular feeder-free condition, the lack of direction or guidance

provided by the specification for culturing the undifferentiated pPS cells under any feeder-free condition, other than the exemplified condition, wherein the undifferentiated pPS cells have been maintained in a culture environment comprising an extracelleular matrix component, it would have required undue experimentation for one skilled in the art to carry out the claimed methods.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, as written, is incomplete. It is unclear how step (b) of the claim, transferring a polynucleotide into pPS cells, relates to the preamble, "A method of obtaining genetically altered pPS cells". There is no indication in the claims that the cells are genetically altered by the mere transfer of a polynucleotide. Note that the polynucleotide recited by the claim fails to state that a promoter is operably linked to the polynucleotide. A promoter is required for the expression of the polynucleotide. The claim is further unclear. The claim recites a method of obtaining genetically altered pPS cells "or progeny thereof". It is unclear if the progeny are genetically altered or progeny of the pPS cells. Claims 2, 3, 5-7 depend from claim 1.

Claim 4, as written, is unclear. The claim recites that the pPS cells are genetically altered by the transferring of a polynucleotide. However, the

polynucleotide is not operably linked to a promoter. A promoter is required for the expression of the polynucleotide.

Claim 10, as written, is unclear. The claim recites the "progeny of such cells". It is unclear what the phrase "such cells" refers back to, undifferentiated cells that are transfected with a polynucleotide, or cells that have differentiated from the transfected undifferentiated cell(s)? Claim 11 depends from claim 10.

Claim 11, as written, is unclear. The claim recites that the population of genetically altered cells are obtained by differentiated the cells of claim 10, however, claim 10 recites 2 cells: the undifferentiated cells that are transfected with a polynucleotide, and the progeny that have inherited the polynucleotide. It is unclear which of the cells claim 11 refers to.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Pedersen [WO 97/47734, published 18 December 1997, Reference AB of the IDS filed 12/6/01, Paper No. 7].

The claims are directed to an undifferentiated human pluripotent stem cell genetically altered with a polynucleotide, a stably transfected undifferentiated human pluripotent stem cell, a population of primate pluripotent stem cells, in which at least 25% of the undifferentiated pPS cells have been transfected with a polynucleotide, or are the progeny of such cells that have inherited the polynucleotide, a population of genetically altered differentiated cells.

Pedersen teach pluripotent stem cells derived from early primate embryos. They teach that these pluripotent stem cells may be genetically modified to have a non-autologous gene [see p. 15, lines 18-35 and 16, lines 13-17]. They teach that the cells may be induced to differentiate [see p. 14-15, bridging ¶].

Accordingly, Pedersen anticipate the claimed invention.

Claims 8-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Gearhart *et al.* [WO 98/43679, published 8 October 1998, Reference AE of the IDS filed 12/6/01, Paper No. 7].

Gearhart teach pluripotent embryonic germ [EG] cells that can be isolated from gonadal tissues, genital ridges, mesenteries or embryonic yolk sacs of human embryos. See pp. 3-4, bridging sentence. Gearhart teaches that the EG cells can be transfected with a transgene that that contains a recombinant polynucleotide that encodes a selectable marker, such that the marker is expressed when the EG cells are allowed to differentiate. See p. 5, lines 9-17. Gearhart teach that the EG cells

can be genetically modified [see p. 19, lines 12-17] and teach methods of introducing a transgene construct into the EG cells [see pp. 20-21]. Gearhart teaches that the transgenic EG cells can be allowed to differentiate to produce transgenic differentiated progeny. See p. 21, lines 4-10.

Note that the specification defines primate pluripotent stem cells as pluripotent cells derived from pre-embryonic, embryonic, or fetal tissue at any time after fertilization and have the characteristic of producing progeny that are derivatives of the three germinal layers. See p. 5, lines 9-13 of the specification. As such, the embryonic germ cells taught by Gearhart anticipate the claimed invention.

Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Dey *et al.* [PNAS, 273:24095-24101 (1998)].

The claim is directed to a population of genetically altered differentiated cells, obtained by differentiating the cells of claim 10. Note that the claim is a product-by-process claim. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or

alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Dey *et al.* teach the transfection of 293 cells [human embryonic kidney] by the plasmid pcDNA-IGF-IR. See p. 24097, 2nd column, *In vivo association of IGF-IR and hSCOS-2 in 293 cells.* As Dey *et al.* teach genetically altered differentiated cells, they anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson [**Science**, 282:1145-1147 (1998), Reference CL of Applicant's IDS filed 12/6/01, Paper No. 7] when taken with Bradley *et al.* [**U.S. Pat. No.** 5,614,396, published March 25, 1997].

The claims are directed to undifferentiated human pluripotent stem cells genetically altered with a polynucleotide. In further embodiments, the pPS cells are human embryonic stem cells.

Thomson teach human blastocyst-derived pluripotent cell lines that have normal karyotypes, express high levels of telomerase activity, and can proliferate in an undifferentiated state for 4-5 months. See Abstract. In particular, Thomson teach that human embryos were cultured to the blastocyst stage and inner cell masses were isolated and cultured. The resulting cells had morphology similar to that of rhesus monkey ES cells, expressed high levels of telomerase activity and expressed cell surface markes that characterize undifferentiated nonhuman primate ES and human EC cells. See p. 1145, col. 2-3. It was found that the cells produced teratomas after injection into SCID mice, and that the teratomas included cells of the endoderm, mesoderm and ectoderm. See p. 1146, 1st column, 2nd full ¶. Thomson do not teach the transfection of the human pluripotent stem cells with a polynucleotide. However, prior to the time the claimed invention was made, Bradley teach methods of transfecting pluripotent human embryonic stem cells. See col. 8, lines 3-24 and lines 34-44.

Accordingly, in view of the combined teachings of Thomson and Bradley, it would have obvious for one of ordinary skill in the art to transfect the human pluripotent stem cells, as taught by Thomson, by the method taught by Bradley, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as supported by Bradley, that transgenic pluripotent stem cells can be easily selected, for example, if they express a selectable marker. See col. 4, lines 26-38.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson [Science, 282:1145-1147 (1998), Reference CL of Applicant's IDS filed 12/6/01, Paper No. 7] when taken with Bradley *et al.* [U.S. Pat. No. 5,614,396, published March 25, 1997], further in view of Tucker *et al.* [Nucleic Acids Res., 25:3745-3746 (1997)].

Thomson teach human blastocyst-derived pluripotent cell lines that have normal karyotypes, express high levels of telomerase activity, and can proliferate in an undifferentiated state for 4-5 months. See Abstract. In particular, Thomson teach that human embryos were cultured to the blastocyst stage and inner cell masses were isolated and cultured. The resulting cells had morphology similar to

that of rhesus monkey ES cells, expressed high levels of telomerase activity and expressed cell surface markes that characterize undifferentiated nonhuman primate ES and human EC cells. See p. 1145, col. 2-3. It was found that the cells produced teratomas after injection into SCID mice, and that the teratomas included cells of the endoderm, mesoderm and ectoderm. See p. 1146, 1st column, 2nd full ¶. Thomson teach that the human pluripotent stem cells are grown on irradiated mouse embryonic stem cells, and that in the absence of the feeder layers, the cells differentiated. See p. 146, 1st col., 2nd full ¶. Thomson do not teach the transfection of the human pluripotent stem cells with a polynucleotide. However, prior to the time the claimed invention was made, Bradley teach methods of transfecting pluripotent human embryonic stem cells. See col. 8, lines 3-24 and lines 34-44.

Neither Thomson nor Bradley teach that the feeder cells which the pPS cells are grown on are drug resistant. However, prior to the time the claimed invention was made, Tucker teach the generation of multiple-drug resistant primary murine embryonic fibroblasts [MEFs]. See *Abstract*. Particularly, Tucker teach that these transgenic MEFs are useful not only for routine maintenance of ES cells, but also in gene targeting experiments, which involve the sequential cultivation of transfected cells in media with different drugs for selection of drug-resistant clones. See p. 3745, 1st column, 1st ¶.

Accordingly, in view of the combined teachings of Thomson, Bradley and Tucker, it would have been obvious for one of skill in the art to culture the pPS

cells, as taught by Thomson, on drug-resistant MEFs for selection of transfected pPS cells, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, because it was an art-recognized goal to produce MEFs which would be used in both gene targeting experiments, and for the maintenance of ES cells, as supported by Tucker, who state that, "Because gene targeting experiments often involve sequential selection for multiple-drug resistance in single ES cell lines, the DR-4 strain represents a suitable and economincal donor for the production of multiple-drug resistant MEFs." See p. 3746, 2nd column, 2nd ¶.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be

submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT

Thái-An N. Ton
Patent Examiner
Group 1632

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630